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Understanding the Diabetic Brain: New Technologies but Old Challenges

Elisabeth A. Northam^{1,2,3} and Fergus J. Cameron^{2,4,5}

Does type 1 diabetes damage the developing brain or not? If so, how and when does this occur, and which brain regions are most vulnerable? These questions have come under increasing scrutiny in the last 20 years as improved technologies and greater success in reducing traditional diabetes complications have allowed us to broaden our therapeutic goals. Many (including the authors) would argue that optimal neural ontogeny is the primary developmental task of childhood and adolescence, as this more than anything else defines our adulthood. The brain is not included in that long list of organ systems that can be repaired or transplanted. Thus, arguably the preeminent measure of the impact of any chronic disease is how it may affect the brain. All the more so when that disease disrupts glucose homeostasis and interferes with the brain's primary metabolic fuel supply.

Recent meta-analysis reviews (1,2) have confirmed subtle decrements in overall IQ in children with type 1 diabetes, as well as in specific skills such as attention, information processing speed, and higher-order executive skills, which are most evident in those with early-onset (<5 years of age) disease. Lower academic achievement in children with type 1 diabetes compared with healthy peers highlights the functional implications of these cognitive deficits (3,4). Thus, although there is now reasonable consensus that cognitive deficits do exist in youth with type 1 diabetes, what causes these deficits is much less clear. Reliable ascertainment of metabolic control history is problematic, particularly in retrospective studies. Furthermore, putative neural insults may be cumulative and/or synergistic, and their impact on central nervous system (CNS) function is likely to be influenced by the stage of neurodevelopment at the time they occur. The timing of events is often poorly documented or indeed unknown, making it even more difficult to disentangle causal relationships between diabetes-related variables and brain changes. The challenge is enormous but clinically important, as even subtle brain changes can have a significant negative impact on a child still acquiring new skills.

New techniques in magnetic resonance imaging have facilitated attempts to define the brain regions most vulnerable to disease effects and to correlate morphological brain changes with cognitive and functional outcomes. Although CNS changes are frequently documented, associations with metabolic control history have been inconsistent. Cross-study comparisons are further limited by varying imaging protocols, varying imaging machines, and varying age-groups (Table 1).

The study by Antenor-Dorsey et al. (5) in this issue of *Diabetes* continues the neuroimaging and diabetes theme undertaken by Perantie, Hershey, and colleagues at St. Louis (6,7) and adds to the mounting body of evidence for CNS involvement in youth with type 1 diabetes. The authors used more sensitive diffusion tensor imaging and fractional anisotropy rather than direct volumetric measurement to determine brain changes. The key finding from this article, studying a predominantly adolescent cohort, is that white matter changes were evident in the superior parietal lobule and thalamus in type 1 diabetic participants compared with sibling control subjects. Participants with a history of three or more episodes of serious hyperglycemia showed specific effects on the superior parietal lobule and the hippocampus. A history of severe hypoglycemic events and chronic poor control were not associated with brain changes. Although the association between hyperglycemia and the superior parietal lobe is broadly consistent with previous findings of Perantie et al. (6), the lack of an association between hypoglycemia and brain changes differs from their previous work that showed an association between recurrent severe hypoglycemia and decreases in occipital/parietal white matter volumes (7). Thus a further novel and important conclusion of this study is the observation that diffusion tensor imaging and volumetric analyses provide different but complimentary information about the integrity of brain structures. The suggestion that the pattern of findings indicates axonal injury rather than a demyelinating process will generate specific hypotheses to be tested in future research. However, although the sample size is robust for a neuroimaging study, the design is retrospective and therefore has all of the limitations inherent in this approach, in particular, reliance on retrospective recall of metabolic control variables and an inability to pinpoint the timing of any neural insults. As Antenor-Dorsey et al. themselves note, it will be important to replicate these findings in a prospective design. In particular, recruitment of a sample at diagnosis with baseline neuroimaging, ongoing monitoring of glycemia and insulin levels, and repeat scanning at regular intervals to document brain changes as they occur will add greatly to our ability to understand the specific neuropathological changes in youth with type 1 diabetes.

New magnetic resonance techniques have assisted our understanding of the impact of type 1 diabetes upon the developing brain, but the old challenge of accounting for

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See accompanying original article, p. 581.

TABLE 1
Summary of brain magnetic resonance studies in type 1 diabetes

Study group	Age range (years)	Mean duration of type 1 diabetes (years)	Group differences in brain volumes		Severe hypoglycemia and brain changes		Chronic hyperglycemia and brain changes	
			GM	WM	GM	WM	GM	WM
Musen et al., 2006 (14)	25–40	20	+	—	+	—	+	—
Weinger et al., 2008 (15)	25–40	22	—	—	+	—	+	+
Perantie et al., 2007 (6)	7–17	5.7	—	—	—	+	+	—
Perantie et al., 2011 (7)	7–17	5.7	—	—	—	+	+	—
Northam et al., 2009 (16)	13–28	13	+	+	+	—	+	—
Pell et al., 2012 (17)	13–28	13	+	+	—	—	—	—
Aye et al., 2011 (18)	3–10	3.6	—	+	+	+	—	—
Kaufmann et al., 2012 (19)	6–20	5.6	+	+	—	—	+	+

GM, gray matter; WM, white matter.

all aspects of dysglycemia remains. To date, we have focused on hypoglycemic or hyperglycemic exposure to explain diabetes-related brain and cognitive changes. Recent in vivo and in vitro studies have shown that other, more subtle aspects of diabetic dysglycemia may be equally relevant. These include glycemic variation (8), fluctuating exogenous insulin levels (9), C-peptide and IGF-1 levels (10), disturbed counter-regulatory hormones (11), and GAD antibody titres (12). Metabolic memory and programming may also affect neural survival (13). Without controlling for all of these various potential influences, attempts to correlate CNS changes with severe episodes of dysglycemia remain a relatively insensitive process.

Until we can more robustly define and quantitate all aspects of the neurotoxic diabetic milieu and measure these in a prospective manner, there will continue to be debate as to which potential cellular insults are most pivotal in affecting neurodevelopment. Variation in neuroimaging and cognitive outcome studies may thus occur by inadvertent comparisons of “apples with oranges” and potentially cause researchers to draw erroneous conclusions. Further, by identifying only those infrequent and severe episodes of dysglycemia, we may simply be measuring the tip of the iceberg. Incorporating the full spectrum of dysglycemia into our explanatory models is an imposing challenge but essential in all clinical studies dealing with pathophysiological cellular mechanisms triggered by dysglycemia and metabolic programming. Notwithstanding the explosion in new imaging techniques to detect change, the old challenge of fully quantifying dysglycemia remains.

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